

# WILMS TUMOR

**Cover image:** Disruption of the differentiation of renal progenitor cells may result in Wilms tumor formation. See page 157, chapter 10 for details. Copyright: Carraro DM, Ramalho RF and Maschietto M.



# WILMS TUMOR

Edited by

**Marry M. van den Heuvel-Eibrink**

Princess Maxima Center for Pediatric Oncology/Hematology,  
Lundlaan 6, 3584 EA Utrecht, The Netherlands



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**Wilms Tumor**

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**Edited by**

Marry M. van den Heuvel-Eibrink, MD, PhD

Princess Maxima Center for Pediatric Oncology/Hematology, Lundlaan 6, 3584

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## Chapter 1

# Wilms' Tumour – Histology and Differential Diagnosis

Sergey D. Popov,<sup>1</sup> Neil J. Sebire,<sup>2</sup> Gordan M. Vujanic<sup>1</sup>

<sup>1</sup>Department of Cellular Pathology, University Hospital of Wales, Cardiff, UK;

<sup>2</sup>Department of Histopathology, Great Ormond Street Hospital, London, UK

**Author for correspondence:** Sergey D. Popov, MD, PhD, Department of Cellular Pathology, University Hospital of Wales, Cardiff CF14 4XW, UK.

Email: [sergey.popov@icr.ac.uk](mailto:sergey.popov@icr.ac.uk); [sergey.popov@wales.nhs.uk](mailto:sergey.popov@wales.nhs.uk)

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## Abstract

Wilms' tumour (WT) is the most common paediatric renal tumour, which can present as a single nodule, as multifocal unilateral lesions or as bilateral tumours. Typically, WT comprises three histological components namely blastemal, epithelial and stromal. The proportion and the degree of maturation of these components vary significantly, making the histological appearance of each tumour unique. Classical triphasic WT rarely presents diagnostic difficulty for pathologists, but when only one component is present, especially in a small biopsy specimen, the differential diagnosis may

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include renal cell carcinoma, metanephric adenoma and hyperplastic nephrogenic rest for epithelial elements and clear cell sarcoma of the kidney, mesoblastic nephroma and synovial sarcoma for stromal elements. Pure blastemal-type WT may be difficult to distinguish from other embryonal ‘small round blue cell tumours’, including neuroblastoma, primitive neuroectodermal tumour/Ewing sarcoma, desmoplastic small round cell tumour and lymphoma. All the three components, though usually blastema, can become anaplastic, leading to the diagnosis of either focal or diffuse anaplasia. WT with diffuse anaplasia and WT with blastemal predominance (after preoperative chemotherapy) are regarded as high-risk tumours and require more aggressive treatment. Careful assessment of the tumour and the normal kidney is critical for accurate subtyping and staging of WT, which is the basis for post-operative treatment. In addition, the identification and correct interpretation of nephrogenic rests may affect prognosis and management. Histological distinction between WT and nephrogenic rest is not always possible based on morphology alone, and implementation of new molecular genetic tools may aid in this regard. Other molecular genetic signatures of WT, such as *P53* mutation and *MYCN* dysregulation, may provide future additional prognostic and therapeutic information.

**Key words:** Nephrogenic rest; Pathology; Wilms’ tumour

## Introduction

Renal tumours comprise 7–8% of all paediatric tumours in children under 15 years of age, and among those, Wilms’ tumour (WT) or nephroblastoma is the most common neoplasm (1). The frequency of renal malignancies in childhood is listed in Table 1.

**Table 1.** Primary renal tumours in childhood

Tumour	Relative frequency (%)
Wilms’ tumour	85
Mesoblastic nephroma	2–3
Clear cell sarcoma	3
Rhabdoid tumour	2
Renal cell carcinoma	5
Others	3

There are several reasons why making correct diagnosis of WT may be challenging for general or paediatric pathologists:

1. Rarity of the paediatric renal tumours results in lack of experience with these entities for most of the pathologists (2)
2. Presence of several subtypes of WT (morphological heterogeneity)
3. Morphological appearances may vary dramatically from case to case
4. Histological patterns of certain WT subtypes may appear initially similar to those of other rare paediatric renal tumours
5. Lack of sharp differential criteria distinguishing WT from nephrogenic rests (NRs), especially in limited biopsy material
6. Assessment of the tumour and determination of the local pathology stage are multi-step and time-consuming processes

Preoperative chemotherapy may create additional difficulty in precise tumour assessment because the criteria for tumour subtyping and risk-group stratification are different for treated and untreated cases (3–5).

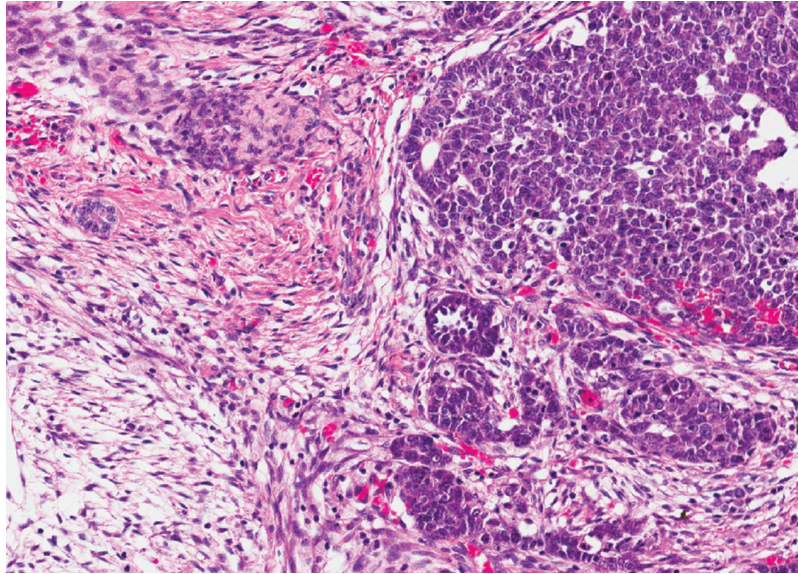
### **Gross appearance**

Macroscopically, WTs are usually large masses disconfiguring the renal contours, which can vary in size significantly. Multicentric tumours occur in 5%, and they are usually associated with NRs (6). Precaution should be taken for the cutting procedure because the cut surface of the tumour may expand from the surrounding pseudocapsule, making the microscopic assessment of tumour margins more difficult. Macroscopic appearance of the cut surface is heterogeneous in many cases, with areas of viable tumour, haemorrhage and necrosis, especially in pre-treated specimens. Viable tumour is usually solid, pale grey to slightly pink or yellow-grey with soft consistency. Some tumours are markedly cystic, and careful search for the presence of solid foci is required. To avoid artificial contamination by the tumour cells, it is important to sample the hilar margins, including vessels, if possible before the tumour is incised.

### **Histological features**

Classical histological features of WT include a triphasic pattern of epithelial, stromal and blastemal components (Figure 1). The proportions of these components and their lines and degree of differentiation vary significantly, resulting in countless tumour appearances. Biphasic and monophasic variants are not uncommon. Preoperative chemotherapy, given to children treated according to the International Society of Paediatric Oncology (SIOP) protocol, may affect the original histology dramatically by reducing or enhancing certain elements or by inducing maturation (7, 8).

Blastema represents the least differentiated, and presumed most malignant, component and consists of small round blue cells with overlapping nuclei and brisk mitotic activity. Several histological

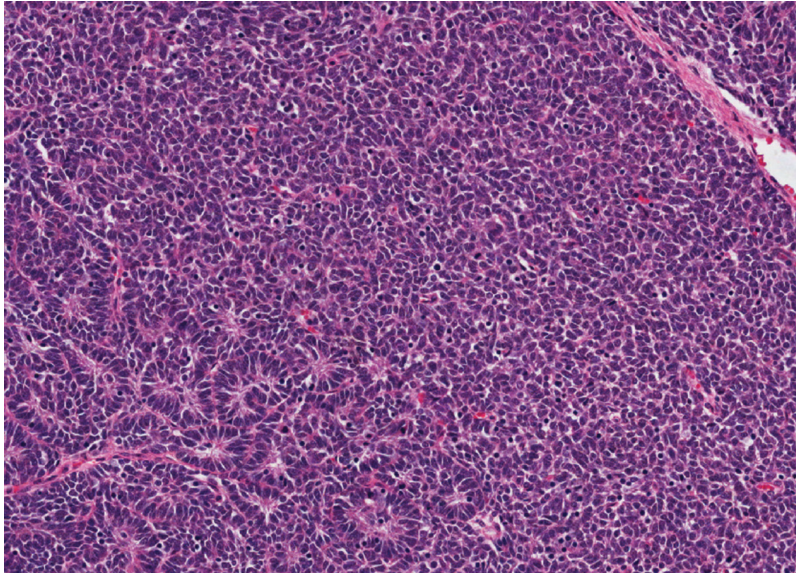


**Figure 1.** Wilms' tumour: mixed pattern with blastema, stroma and single epithelial structures.

patterns of blastema, including diffuse, serpentine, nodular and basaloid, have been described. The serpentine pattern of growth is characterised by broad bands of undifferentiated cells surrounded by fibromyxoid stroma. In the basaloid variant, nests or cords of blastema have a distinctive peripheral palisading of elongated cells with epithelial differentiation. All four above-mentioned patterns may be found in the same tumour and have no prognostic significance; however, their recognition in the histological slides can be helpful in differential diagnosis with other 'small round blue cell tumours' when the tumour is composed of the blastemal component only. It is worth noting that although WT's are mostly well circumscribed and surrounded by a pseudocapsule, which is used as one of the differential diagnostic criteria, blastemal-type WT's, usually with diffuse growth pattern, can show marked infiltrative growth with no pseudocapsule between the tumour and adjacent tissues. Primitive tubular epithelial structures sometimes present in the centre of blastemal nodules may morphologically mimic neuroblastoma-like areas with pseudorosettes. Vague epithelioid or spindle cell appearances are other possible histological features of blastema depending on the extent and pattern of early differentiation. There are no strict criteria to discriminate blastema from early epithelial differentiation (Figure 2) or stromal lineage, with almost all literature describing WT subtypes being based on subjective morphological criteria.

The epithelial component may demonstrate the whole spectrum of differentiation from early stages of tubular formation with primitive epithelial rosette-like structures to somewhat differentiating tubules or glomeruli-like structures, reflecting different stages of nephrogenesis. Squamous epithelial islands and mucinous epithelium are examples of heterologous differentiation within the epithelial component of WT.



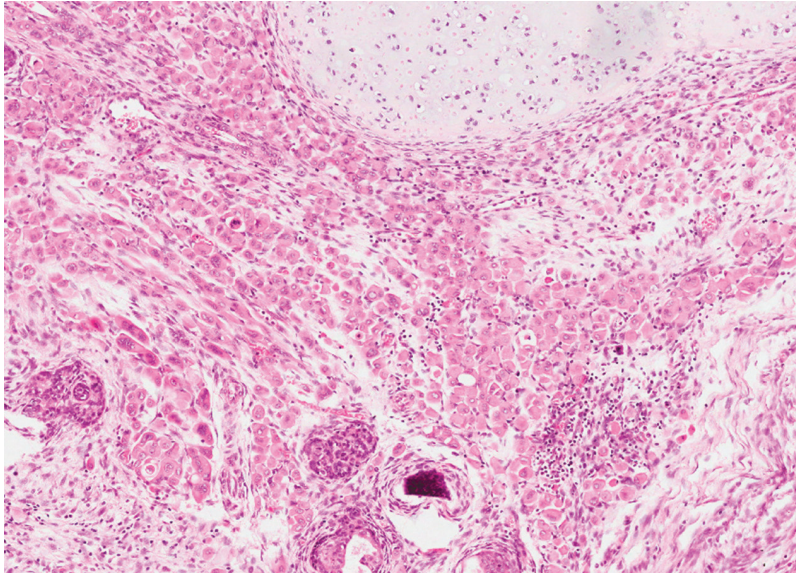


**Figure 2.** Blastemal-type Wilms' tumour with early epithelial differentiation.

The stromal component may include densely packed undifferentiated mesenchymal cells or loose cellular myxoid areas. The latter areas may be difficult to distinguish from non-tumorous stroma associated with chemotherapy-induced change (CIC). Heterologous differentiation of neoplastic stroma in the form of well-differentiated smooth or skeletal muscle cells, fat tissue, cartilage, bone and even glial tissue is present in some cases, especially in tumours that have undergone preoperative chemotherapy (Figure 3).

CIC includes areas of necrosis, haemorrhage and fibrosis of varying degree and areas with foamy and/or haemosiderin-laden macrophages. Primitive, highly proliferative blastemal component more readily responds to chemotherapy, leaving homogeneous eosinophilic areas where 'shadows' of pre-existing cells and structures may be seen. Mature epithelial and stromal components are often less sensitive to chemotherapy, and such tumours may show no significant response to pre-operative therapy in terms of tumour-size shrinkage. It is worth emphasising that the criteria and terminology used by the SIOP and National Wilms' Tumor Study/Children's Oncology Group (NWTs/COG) differ, so direct comparison of certain subtypes is not feasible. Histological assessment of tumour responsiveness to chemotherapy is important for risk-group stratification by the SIOP. For instance, completely necrotic WT is regarded as a low-risk tumour and requires less post-operative therapy than WTs from other groups. Further, stromal- or epithelial-type WTs are terms used by the SIOP for pre-treated tumours, whereas the NWTs/COG uses terms such as stromal or epithelial





**Figure 3.** Preoperatively treated Wilms' tumour with prominent skeletal muscle differentiation and cartilage.

predominant WT (Table 2). In non-treated cases, stromal or epithelial predominant tumours may contain up to one-third of the blastemal component, whereas in pre-treated cases, the finding of >10% of blastema would result in the tumour being sub-classified as mixed type (9).

*Anaplastic Wilms' tumours* account for 5–8% of all WTs, and the majority of patients with anaplastic WT (Figure 4) are older than those with non-anaplastic WT. The criteria necessary for the diagnosis of anaplasia are the presence of large, atypical multipolar mitotic figures and significantly enlarged and hyperchromatic nuclei (10). These tumours are generally aneuploid. Anaplasia may be focal or diffuse. Focal anaplasia means that there is a localised and definitely completely excised area with anaplastic features. All other cases where anaplasia is found should be regarded as diffuse anaplasia. Diffuse anaplasia is regarded as the only unfavourable histological feature in WTs undergoing primary nephrectomy. Anaplasia is responsible for adverse outcome, especially in the cases with advanced tumour stage; thus, its recognition is essential for the prognosis and treatment. Because anaplasia is regarded as a chemo-resistant cell clone, it may be easier to detect it in pre-treated cases due to loss of other chemo-sensitive elements. Anaplastic tumours often express p53 on immunohistochemical staining and bear mutants in the *TP53* gene (11–14). *TP53* mutation has been shown to compromise patients' survival, overall and event-free, and therefore has the potential as an adverse prognostic factor combined with anaplastic

**Table 2.** Current SIOP classification of paediatric renal tumours

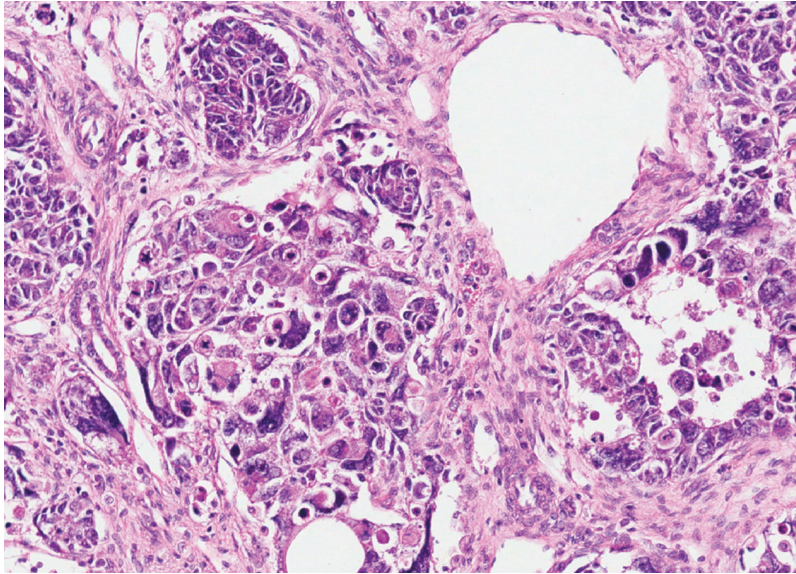
Pre-treated tumours*	Primary nephrectomy tumours
Low risk	Low risk
Mesoblastic nephroma	Mesoblastic nephroma
Cystic partially differentiated nephroblastoma	Cystic partially differentiated nephroblastoma
Completely necrotic nephroblastoma	
Intermediate risk	Intermediate risk
Nephroblastoma – epithelial type	Non-anaplastic nephroblastoma and its variants
Nephroblastoma – stromal type	Nephroblastoma – focal anaplasia type
Nephroblastoma – mixed type	
Nephroblastoma – regressive type	
Nephroblastoma – focal anaplasia type	
High risk	High risk
Nephroblastoma – blastemal type	Nephroblastoma – diffuse anaplasia type
Nephroblastoma – diffuse anaplasia type	Clear cell sarcoma of the kidney
Clear cell sarcoma of the kidney	Rhabdoid tumour of the kidney
Rhabdoid tumour of the kidney	

\*The criteria for subclassifying pre-treated WTs are as follows: completely necrotic type shows no viable tumour elements. If more than 66% (two-thirds) of the tumour is non-viable (i.e., shows chemotherapy-induced changes), it is regarded as regressive type, irrespective of the presence of remaining viable tumour components. If viable tumour comprises more than one-third of the tumour mass, subtyping depends on the percentage of viable components: in mixed type, none of the components comprise more than 66% of the tumour; in epithelial (or stromal) type, in addition to having more than 66% of the tumour being composed of epithelial (or stromal) elements, the finding of only up to 10% of blastema is allowed (if the finding is more, then the tumour is subclassified as mixed type).

morphological features (15). Dysregulation of *MYCN* gene in WTs with anaplastic histology has also been reported to be involved in the development of tumours with adverse outcome (16).

### Handling of the nephrectomy specimen

Core biopsies are done in some cases, and their main purpose is to confirm whether a tumour is a WT, in order to give appropriate pre-operative chemotherapy. If biopsies contain enough



**Figure 4.** Wilms' tumour with anaplasia.

tissue for diagnostic purpose, some material should be kept frozen for molecular biology studies.

Immediately after surgery, the tumour should be delivered to the pathology department for appropriate handling of the specimen. Careful assessment of the surface and of the margins of renal vessels and the ureter and the assessment of the renal capsule for breaches are critical points for adequate staging (17). The nephrectomy specimen should be inked after photography and measurement. After opening (bivalving), tumour and normal renal tissues are taken for biological studies. Additional parallel slices are usually needed for a large tumour, but they should not compromise staging assessment of the fixed neoplasm. Careful mapping of the specimen, photographs and precise block guides are crucial in the staging assessment. At least one whole longitudinal slice of the tumour is sampled, with additional blocks taken from grossly different areas. When multicentric tumour is present, each nodule is sampled for histology and molecular biology study. Interface between the tumour and normal kidney as well as blocks containing renal and tumour capsule are always taken for histological examination. Evaluation of the renal sinus involvement is very important for the staging purpose; hence, this part of the specimen is a subject of thorough investigation especially when the tumour compromises the normal sinus architecture (18). The residual kidney is also sampled for possible presence of NRs. The hilar fat and all lymph nodes are sampled in search for possible metastases.

Current staging criteria for pre-treated and non-treated tumours are shown in Tables 3 and 4. The presence of tumour cells in the vessels within the tumour mass does not generally change the stage unless it is found in the vessels of the renal sinus. The finding of non-viable tumour and/or secondary inflammatory changes in the renal sinus or perirenal fat is not the criterion for stage II. However, the finding of non-viable tumour at the resection margins is currently regarded as a reason for stage III in the SIOP protocol (9). The presence of Tamm-Horsfall protein and mature tubules in lymph nodes is occasionally seen, but it should not be regarded as an evidence of metastatic disease (19). Recent studies have shown that there is considerable discrepancy in diagnosing and staging of these tumours between the institutional pathologists and the central pathology reviewers (around 20% of cases), so rapid central pathology review is being introduced and recommended in renal tumour trials (2, 20, 21).

**Table 3.** SIOP staging system

WT 2001 staging criteria for pre-operatively chemotherapy-treated tumour*
<p><i>Stage I</i></p> <ul style="list-style-type: none"> <li>a. The tumour is limited to the kidney or surrounded with a fibrous pseudocapsule if outside the normal contours of the kidney. The renal capsule or pseudocapsule may be infiltrated by the tumour, but it does not reach the outer surface</li> <li>b. The tumour may be protruding ('bulging') into the pelvic system and 'dipping' into the ureter, but it is not infiltrating their walls</li> <li>c. The renal sinus (its vessels and soft tissues) is not involved</li> <li>d. Intrarenal vessels may be involved</li> </ul> <p><i>Notes: Fine-needle aspiration or percutaneous core needle biopsy does not upstage the tumour, but the size of the needle gauge should be mentioned to the pathologist</i>  <i>The presence of necrotic tumour or chemotherapy-induced change in the renal sinus and/or within the perirenal fat should not be regarded as a reason for upstaging the tumour, provided it is completely excised and does not reach the resection margins</i></p>
<p><i>Stage II</i></p> <ul style="list-style-type: none"> <li>a. Viable tumour penetrates through the renal capsule and/or fibrous pseudocapsule into perirenal fat but is completely resected (resection margins 'clear')</li> <li>b. Viable tumour infiltrates the soft tissues and/or blood and/or lymphatic vessels of the renal sinus</li> <li>c. Viable tumour infiltrates the perirenal tissue, but it is completely resected</li> <li>d. Viable tumour infiltrates the renal pelvic or ureter's wall</li> <li>e. Viable tumour infiltrates adjacent organs or vena cava but is completely resected</li> </ul> <p><i>Notes: Infiltration of the adrenal gland is not regarded as stage II if there is a (pseudo)capsule. Equally, tumour adherence to the liver is not regarded as stage II for which there should be a genuine infiltration of the liver parenchyma</i></p>

(Continued)

**Table 3.** (Continued)

WT 2001 staging criteria for pre-operatively chemotherapy-treated tumour*
<p><i>Stage III</i></p> <ul style="list-style-type: none"> <li>a. Viable or non-viable tumour present at resection margins</li> <li>b. Any abdominal lymph nodes are involved</li> <li>c. Tumour rupture before or intraoperatively (irrespective of other criteria for staging)</li> <li>d. Tumour penetration through the peritoneal surface</li> <li>e. Tumour implants are found on the peritoneal surface</li> <li>f. Tumour thrombi present at resection margins of extra-renal vessels, transected or removed piecemeal by the surgeon</li> <li>g. The tumour has been surgically biopsied (wedge biopsy) prior to preoperative chemotherapy or surgery</li> </ul> <p><i>Note: The presence of necrotic tumour or chemotherapy-induced changes in a lymph node or at the resection margins is regarded as a proof of previous tumour with microscopic residue, and therefore, the tumour is assigned stage III (because of the possibility that some viable tumour is left behind in the adjacent lymph node or beyond the resection margins)</i></p>
<p><i>Stage IV</i></p> <ul style="list-style-type: none"> <li>a. Haematogenous metastases (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdominopelvic region</li> </ul>
<p><i>Stage V</i></p> <ul style="list-style-type: none"> <li>a. Bilateral renal tumours at diagnosis. Each side should be substaged according to the above criteria</li> </ul>

\*Data from reference (9) with additional notes for stage II.

### Nephrogenic rests and nephroblastomatosis

NRs are abnormal areas of embryonic tissue persisting beyond 36 weeks of development. They are found in 30–44% of kidneys with WT. The term ‘nephroblastomatosis’ was introduced in 1961 by Hou and Holman (22) in their description of a lesion composed of immature renal tissue in the kidney of a premature infant. Later, the term was adopted by Beckwith et al. (23) and Beckwith (24) who developed the theory of WT origin from NR.

There are two main types of NR – perilobar (PLNR) and intralobar (ILNR). The former is located at the periphery of the renal lobules and the latter in the central part of the lobe. ILNR is believed to arise earlier in the development when compared with PLNR, which may explain the higher frequency of heterologous elements in ILNR, such as striated muscle, fat, cartilage and bone. Depending on the stage of their development, both ILNR and PLNR might present with different morphological patterns. Beckwith suggested several histological types, including incipient (in newborns and young infants) or dormant (in older infants or children), regressing or sclerotic, obsolescent, and hyperplastic NR.



**Table 4.** COG staging system

WT staging criteria for non-treated tumours prior to operation*	
<i>Stage I</i>	<ul style="list-style-type: none"> <li>a. Tumour limited to the kidney and completely resected</li> <li>b. Renal capsule intact</li> <li>c. The tumour was not ruptured or biopsied prior to removal</li> <li>d. Renal vein contains no tumour (intrarenal vessel involvement may be present)</li> <li>e. No residual tumour apparent beyond the margins of excision</li> </ul>
<i>Stage II</i>	<ul style="list-style-type: none"> <li>a. Tumour extends beyond the kidney but is completely resected</li> <li>b. Regional extension of tumour (vascular invasion outside the renal parenchyma or within the renal sinus and/or capsular penetration with negative excision margin)</li> <li>c. Operative tumour spill confined to flank (no peritoneal contamination)</li> <li>d. Tumour biopsy (except fine-needle aspiration) prior to surgery</li> </ul>
<i>Stage III</i>	<ul style="list-style-type: none"> <li>a. Non-haematogenous metastases confined to the abdomen (e.g., tumour in regional lymph nodes), including tumour implants on or penetrating the peritoneum</li> <li>b. Gross or microscopic tumour remains post-operative (tumour at the margins of resection)</li> <li>c. Tumour spill before or during surgery not confined to flank</li> <li>d. Piecemeal excision of the tumour (removal in &gt;1 piece)</li> </ul>
<i>Stage IV</i>	<ul style="list-style-type: none"> <li>a. Presence of haematogenous metastases or metastases to distant lymph nodes</li> </ul>
<i>Stage V</i>	<ul style="list-style-type: none"> <li>a. Bilateral renal involvement at the time of initial diagnosis</li> </ul>

\*Data from reference (3).

The presence of multifocal NRs is defined as nephroblastomatosis. In the condition called diffuse hyperplastic perilobar nephroblastomatosis, which is often bilateral, a large portion of the cortical renal parenchyma is replaced with a thick 'crust' composed of proliferating nephroblastic tissue. It is important to distinguish NR from WT because their clinical management differs significantly. The usual differential diagnostic guides emphasise the criteria such as a lack of fibrous pseudocapsule in NR, which is almost always present in WT cases (Figures 5 and 6). This observation provides a useful tool for pathologists dealing with untreated nephrectomy specimens. However, for patients treated according to the SIOP protocol receiving pre-operative chemotherapy, a fibrous capsule may be present even around the foci of NRs. Conversely, blastemal-type WT may show no separation from the renal parenchyma by the pseudocapsule. In addition, because their microscopic features may be very similar, distinguishing WT from NR in limited needle biopsy material is virtually impossible. In such cases, it has been suggested to use the term

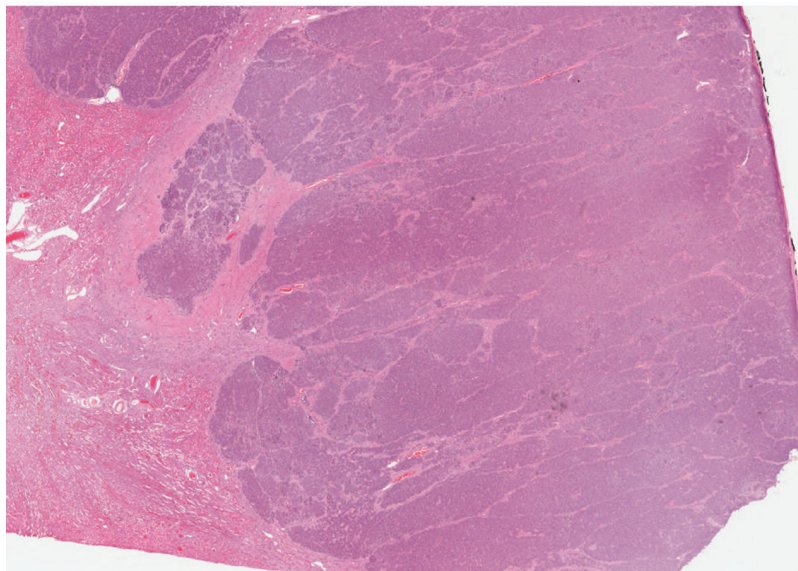
‘nephroblastic process, consistent with either WT or NR’ as optimal, with further radiologic-pathologic correlation being required (25). The main differential diagnostic criteria for NR and WT are summarised in Table 5, but one has to bear in mind that none of them is absolutely conclusive.

Another challenge for pathologists is to assess the local stage of the tumour in the presence of ILNR. Providing the frequent location of the ILNR next to the renal sinus or even in the sinus or in the calyceal wall can be misinterpreted as renal sinus invasion by the tumour, leading to upstaging and unnecessary more aggressive treatment.

There are no reliable immunohistochemical or molecular markers facilitating differential diagnosis of NR and WT. A recent study showed significant variability of methylation profiles in NRs and WTs and reported changes in the methylome to underlie NR formation and transformation to WTs in a subset of cases (26). These data have the potential for being implemented into the clinical differential diagnosis of these two lesions, but more extensive work is required.

### Differential diagnosis

The diagnosis is usually straightforward in triphasic or even biphasic WTs, although their subclassification may be challenging (27). However, monophasic WTs may be very difficult



**Figure 5.** View of treated case of hyperplastic perilobar nephroblastomatosis. Partially developed fibrous capsule is seen.

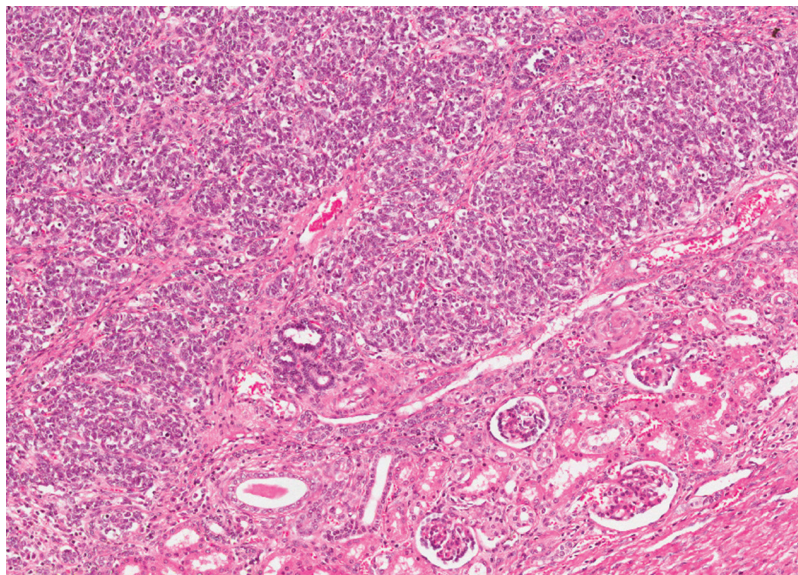
**Table 5.** Features of NR and WT

WT	NR
Shape – spherical	Shape – oval
Fibrous capsule is present	No fibrous capsule*
Skeletal muscle differentiation is common	Skeletal muscle differentiation is uncommon
Usually solitary	Often multifocal

NR, nephrogenic rest; WT, Wilms' tumour.

\*In untreated cases but in pre-treated cases, capsule may be present.

to separate from other renal tumours with similar histological features. Pure blastemal-type WTs have to be distinguished from other undifferentiated tumours, such as neuroblastoma, primitive neuroectodermal tumour/Ewing sarcoma of the kidney (28), desmoplastic small round cell tumour (29) and synovial sarcoma (30). It is particularly important to consider non-WTs in older patients (Table 5) and adults – WT in adults definitely exists, but many of the renal tumours that in the past were labelled as adult WTs proved to be some of the mentioned entities. In order to reach the correct diagnosis in such cases, it is critical to apply immunohistochemistry and molecular biology investigations looking for characteristic features. Although blastemal components may show focal CD99 positivity, it



**Figure 6.** Hyperplastic perilobar nephroblastomatosis – direct interface with normal renal parenchyma with no pseudocapsule.



is usually not diffuse and membranous as in Ewing sarcoma of the kidney, where genetic studies also show characteristic translocations, with t(11;22)(q24;q12) being the most common (28). Desmoplastic small round cell tumour shares many immunohistochemical features with blastemal-type WT but is rare, and the diagnosis should only be made if genetic investigations demonstrate the *EWS-WT1* t(11;22)(q13;q12) translocation(29). Neuroblastoma usually shows elevated levels of catecholamines, and on histological examination, its cells reveal non-overlapping nuclei and coarse 'salt and pepper' chromatin. Both tumours may be positive for neuron-specific enolase and CD56, but WT1 marker is negative in neuroblastoma and NB84a marker is negative in WT. In the past, in rare cases, a rhabdoid tumour could be mistaken for a WT, but now it is simple to distinguish between them based on immunohistochemistry, with the lack of nuclear INI1 expression in rhabdoid tumour (31). Pure epithelial-type WT may be difficult to distinguish from metanephric adenoma, renal cell carcinoma and hyperplastic PLNR. Highly differentiated epithelial-type WT may be composed of small, well-differentiated and closely packed tubules similar to metanephric adenoma, but the latter can be diagnosed by the lack of capsule between the tumour and renal parenchyma and the absence of mitotic activity. The combination of CK7-, AMACR-, WT1+ and CD57+ has been shown as an immunohistochemical pattern of metanephric adenoma (32). Renal cell carcinomas in children associated with translocations show distinctive histological features, but papillary renal cell carcinoma (as seen in adults) may be more challenging to diagnose. Immunohistochemistry demonstrating the expression of markers such as CK7 and CD10 (33, 34) and cytogenetic findings may be very helpful (35).

In the differential diagnosis of pure stromal-type WTs, a clear cell sarcoma of the kidney and mesoblastic nephroma should be considered. In WTs treated with preoperative chemotherapy, the stroma may show a striking clear cell sarcoma-like appearance, and extensive sampling may be required in order to find the foci with other WT components.

WT with prominent cystic appearance has to be differentiated from cystic nephroma (CN) and cystic partially differentiated nephroblastoma(CPDN). CN and CPDN share some clinical-pathological features and were regarded as related lesions. They occur in young children, are well demarcated from the kidney and are composed of cysts only, with no solid nodules. Histologically, the only difference between these lesions is the finding of blastema in the septa of CPDN, whereas CN contain no blastema (36). However, despite clear similarities, recent studies showed that these lesions are not related at all and that CN shows DICER1 mutations that are never found in CPDN or WT (37). Still, both CN and CPDN are adequately treated with resection alone, with an excellent prognosis and no chemotherapy required, whereas cystic WTs, which are usually stage I and therefore having a fairly good

**Table 6.** Age and likely renal tumour\*

Age (years)	Most common	Possible	Rare
Birth	MN	WT	RTK
<1	WT, MN	RTK, CCSK	
1–5	WT	CCSK	MN (<3 years), RTK
5–10	WT	CCSK, RCC	
11–15	WT, RCC	PNET	

\*Data from reference (9).

CCSK, clear cell sarcoma of the kidney; MN, mesoblastic nephroma; PNET, primitive neuroectodermal tumour; RCC, renal cell carcinoma; RTK, rhabdoid tumour of the kidney; WT, Wilms' tumour.

prognosis, should be treated according to the current protocol for WT. Although CN is a benign neoplasm, its association with the malignant pleuropulmonary blastoma has been reported recently (38).

Awareness of the age distribution for paediatric kidney tumours (Table 6) might assist in their differential diagnosis (39–41).

## Conclusion

Remarkable progress in classification, treatment and understanding of the pathology and molecular biology of WT has been made over recent decades. Because this tumour is rare, it still represents a diagnostic problem, and awareness of the potentially complex pathological features of this malignancy is required for the accurate diagnosis, subtyping and staging to allow appropriate treatment. Preoperative chemotherapy may affect histological and staging features, and diagnostic pathologists should be familiar with these when assessing such tumours. Adequate handling and sampling are essential prerequisites for correct diagnosis. Molecular biology markers are likely to play an even more important role in the tumour prognosis and differential diagnosis in future, but at present, pathological examination represents the gold standard for diagnosis, subtyping and prognosis.

## Conflict of Interest

The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this article.

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